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10/565,238

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FISHMAN19B

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EXAMINER

SINGH, SATYENDRA K

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/565,238	<b>Applicant(s)</b> FISHMAN ET AL.	
	<b>Examiner</b> SATYENDRA K. SINGH	<b>Art Unit</b> 1657	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on 08 September 2009.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 15-28 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 15-28 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### DETAILED ACTION

**The final action mailed by the examiner on 5/8/09 has been vacated** (see interview summary, dated 10/9/09), and a new office action is provided herein.

Applicant's response filed on 9/8/09 is duly acknowledged.

#### ***Rejoinder of Withdrawn groups***

The restriction/election between the inventions of groups III and IV (claims 15-20 and 21-28, respectively) are hereby withdrawn. The two groups have been rejoined for examination purposes herein.

Claims 15-20 (elected invention of group III) and newly added claims 21-28 are currently examined in this application.

The following contains **new ground of rejections** necessitated by applicant's current amendments to pending claims.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

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4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names **joint inventors**. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 15-28 (as amended) are rejected under 35 U.S.C. 103(a) as being unpatentable over Gessi et al (September 2004; IDS; citation AS) taken with Rhodes & Campbell (2002; [U]) and in view of Montesinos et al (2003; IDS, citation AQ) and Fishman & Bar-Yehuda (2003; [V]).

Claims are directed to a method for selecting a subject in an inflammatory state that is the result of an autoimmune disease, which subject is suitable for anti-inflammatory therapeutic treatment by means of an A<sub>3</sub> adenosine receptor (A<sub>3</sub>AR) agonist (or a method for determining the probability that a selected subject in an inflammatory state that is the result of an autoimmune disease, will respond to anti-inflammatory therapeutic treatment by means of an A<sub>3</sub>AR agonist), the method comprising: determining the level of expression of A<sub>3</sub>AR in a sample of white blood cells (WBCs) of the subject and selecting the subject as being suitable to receive said anti-inflammatory therapeutic treatment if said level is above a predefined threshold that is above the level of A<sub>3</sub>AR expression in WBCs of a healthy subject; wherein said sample of WBC is taken from a subject before receiving an anti-inflammatory treatment; and wherein said predefined threshold is a multiple of the level of A<sub>3</sub>AR expression in the WBCs of a healthy subject.

Gessi et al disclose a method for selecting a subject (i.e. a method for diagnosing a patient; see abstract, page 5895; “*Conclusions*”, in particular) in an inflammatory state (see evidentiary prior art disclosure of Rhodes & Campbell, wherein they disclose colorectal cancer and its association with inflammation, and the fact that a patient suffering from colorectal cancer is a subject in “an inflammatory state”; see page 10,

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figure 2, pages 13 and 15, in particular), the method comprising: determining the level of expression of A<sub>3</sub>AR in a sample of white blood cells (WBCs) of the subject (see; Gessi et al, determination of A<sub>3</sub>AR levels by receptor binding assays in peripheral blood cells such as lymphocytes and neutrophils, protein levels confirmed by immunohistochemistry; page 5898, table 3, in particular), wherein said sample of WBC is taken from a subject before receiving an anti-inflammatory treatment (such as before a surgical resection; see Gessi et al, abstract, and page 5896, in particular); and wherein said predefined threshold is a multiple of the level of A<sub>3</sub>AR expression (3-fold in terms of receptor density when compared with healthy subjects; see Gessi et al, abstract, in particular) in the WBCs of a healthy subject (see also Gessi et al, page 5898, table 3 and figure 2, in particular).

However, the method step of selecting the subject as being suitable to receive said anti-inflammatory therapeutic treatment (or determining that there is a greater probability that the subject will respond to said anti-inflammatory therapeutic treatment) by means of an A<sub>3</sub> adenosine receptor (A<sub>3</sub>AR) agonist if said level is above a predefined threshold that is above the level of A<sub>3</sub>AR expression in WBCs of a healthy subject; and wherein the inflammatory state is result of **an autoimmune disease** such as **rheumatoid arthritis (RA)**, is not explicitly disclosed by Gessi et al taken with Rhodes & Campbell.

Fishman & Bar-Yehuda disclose the pharmacology and therapeutic applications of A<sub>3</sub> receptor subtype, especially the use of agonists such as IB-MECA (N<sup>6</sup>-(3-iodobenzyl)-adenosine-5'-N-methyluronamide; see page 463, abstract and introduction, in particular) as most potent therapeutic agents for the treatment of inflammation, wherein they disclose the fact that the anti-inflammatory response is mediated upon A<sub>3</sub>AR activation in neutrophils, eosinophils and macrophages (i.e. white blood cell components) via direct effect on the production of anti-inflammatory cytokines (see

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page 464, right column, in particular). Thus, Fishman & Bar-Yehuda clearly suggest the use of agonist such as IB-MECA for activation of A<sub>3</sub>AR receptor to produce desired anti-inflammatory effects in subjects in need thereof, including in clinical settings for therapeutic treatment.

Montesinos et al disclose the role of A<sub>3</sub>AR receptors, the activation of which is required for the inhibition of inflammation (i.e. for anti-inflammatory therapeutic treatment) by methotrexate commonly used for the therapy of chronic inflammatory diseases, including autoimmune joint disorders such as RA (see page 240, in particular).

Thus, given the detailed disclosures in the cited prior art at the time of claimed invention, it would have been obvious to a person of ordinary skill in the art to modify the method of Gessi et al such that the subject is selected as being suitable to receive said anti-inflammatory therapeutic treatment by means of an A<sub>3</sub>AR agonist (or determining the probability that a selected subject in an inflammatory state that is the result of an autoimmune disease, will respond to anti-inflammatory therapeutic treatment by means of an A<sub>3</sub>AR agonist) if said level is above a predefined threshold that is above the level of A<sub>3</sub>AR expression in WBCs of a healthy subject, wherein the inflammatory state is result of an autoimmune disease such as rheumatoid arthritis, as clearly suggested and implicated by the combined teachings of the cited prior art references of Fishman & Bar-Yehuda and Montesinos et al.

One of ordinary skill in the art would have been motivated to do such modification in the method of Gessi et al because the disclosures of both Fishman & Bar-Yehuda

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and Montesinos et al strongly implicate A<sub>3</sub>AR receptor activation and its role anti-inflammatory treatment in patients with inflammation (such as RA or other inflammatory diseases), especially using the well known A<sub>3</sub>AR agonists such as IB-MECA, with reasonable expectation of success (see disclosures of Fishman & Bar-Yehuda, in particular). Thus, an artisan of ordinary skill in the art, at the time this invention was made, would have fully contemplated the implications and teachings from the cited prior art that provide the nexus between the over-expression of A<sub>3</sub>AR receptor in peripheral white blood cells (such as lymphocytes, neutrophils, etc. as taught by Gessi et al) and inflammatory state of a subject that is suitable to receive the anti-inflammatory treatment (for determining the probability that a selected subject in an inflammatory state that is the result of an autoimmune disease, will respond to anti-inflammatory therapeutic treatment by means of an A<sub>3</sub>AR agonist, including as a candidate for treatment under clinical studies) by means of an A<sub>3</sub>AR agonist such as IB-MECA, as explicitly suggested in the cited prior art.

Thus, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill in the art at the time the claimed invention was made.

As per MPEP 2111.01, *during examination, the claims must be interpreted as broadly as their terms reasonably allow. In re American Academy of Science Tech Center, F.3d, 2004 WL 1067528 (Fed. Cir. May 13, 2004)(The USPTO uses a different standard for construing claims than that used by district courts; during examination the USPTO must give claims their broadest reasonable interpretation.). This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).*

### ***Response to Arguments***

Applicant's arguments filed on 9/8/09 have been fully considered (as they pertain to the prior art rejection of record over claims 15-21) but they are not persuasive for the following reasons of record:

Applicant's arguments regarding the restriction/election between groups III and IV have been deemed persuasive. The groups (claims 15-21 and 22-28) have been rejoined and examined as discussed above in the obviousness rejection of record.

Regarding the obviousness rejection of record of pending claims 15, 16 and 18-21 over the cited prior art combination (Gessi et al taken with Rhodes & Campbell, and in view of Montesinos et al and Fishman & Bar-Yehuda), applicants argument (see remarks, pages 10-13) that "*...the method of selecting an autoimmune disease patient that is most suitable for treatment with an A<sub>3</sub>AR agonist is nowhere taught or suggested by any of the references of record, either alone or in combination. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged*" is fully considered. However, it is not found to be persuasive because Gessi et al clearly disclose the diagnostic use of elevated levels of A<sub>3</sub>AR in peripheral blood cells (including white blood cells such as lymphocytes and neutrophils, measured using a receptor binding assay) of patients with an inflammatory state (albeit as a result of the colorectal cancer). The cited reference of Fishman & Bar-Yehuda clearly suggest the therapeutic applications of A<sub>3</sub> receptor subtype, especially the use of agonists such as IB-MECA as one of the most potent therapeutic agents for the treatment of inflammation, which is believed to be mediated upon A<sub>3</sub>AR activation in neutrophils,

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eosinophils and macrophages (i.e. white blood cell components) via direct effect on the production of anti-inflammatory cytokines (see page 464, right column, in particular).

Therefore, suggesting the use of agonist IB-MECA for activation of A<sub>3</sub>AR receptor to produce desired anti-inflammatory effects in subjects in need thereof, including its use in clinical settings. Montesinos et al, on the other hand, disclose the role of A<sub>3</sub>AR receptors, the activation of which is required for the inhibition of inflammation (i.e. for anti-inflammatory therapeutic treatment) by methotrexate commonly used for the therapy of chronic inflammatory diseases, including autoimmune joint disorders such as Rheumatoid Arthritis, thus clearly providing the nexus for the diagnostic or predictive (i.e. determining that there is a greater probability that the subject will respond to said anti-inflammatory therapeutic treatment) use of A<sub>3</sub>AR receptor levels in white blood cells in patients (that can be suitably treated with the A<sub>3</sub>AR agonist IB-MECA) having inflammatory state as a result of autoimmune disease, for example, Rheumatoid Arthritis.

The argument (see remarks, page 12, in particular) that "*While Fishman and Montesinos relate to the use of an A<sub>3</sub>AR agonist in the treatment of autoimmune diseases, there is no suggestion therein that the level of A<sub>3</sub>AR expression in white blood cells of autoimmune patients may be used as a diagnostic for the presence of autoimmune disease, as Gessi does with respect to colon carcinoma*" is noted and fully considered. However, it is not found to be persuasive because the combined teachings of the cited references of record clearly suggest a link (i.e. nexus) between inflammation in patients (as a result of inflammatory states such as colorectal cancer and

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autoimmune diseases such as rheumatoid arthritis), the levels of A<sub>3</sub>AR receptor in peripheral blood cells such as white blood cells, and the use of A<sub>3</sub>AR agonist such as IB-MECA as an anti-inflammatory drug in clinical settings, and therefore, the methods as currently claimed (see specific recitations of instant claims 15 and 22, in particular) would have been obvious to an artisan of ordinary skill in the clinical art, at the time the claimed invention was made.

The obviousness rejection of record is therefore deemed proper.

### ***Conclusion***

#### ***NO claims are allowed.***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to SATYENDRA K. SINGH whose telephone number is (571)272-8790. The examiner can normally be reached on 9-5MF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Satyendra K. Singh/  
Examiner, Art Unit 1657

/JON P WEBER/

Supervisory Patent Examiner, Art Unit 1657